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REVIEW

Obesity-related thyroid reflections: from weight gain to weight loss

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Abstract

Obesity and thyroid disorders are highly prevalent conditions with complex, bidirectional interactions. Thyroid hormones, particularly triiodothyronine, regulate energy expenditure, thermogenesis, and lipid metabolism, while excess adiposity can modulate hypothalamic–pituitary–thyroid (HPT) axis activity. Individuals with obesity frequently exhibit elevated thyroid-stimulating hormone (TSH) levels in the absence of true thyroid disease, suggesting an adaptive rather than pathological response. The balance of current evidence suggests that non-autoimmune hyperthyrotropinemia predominates in severe and morbid obesity, whereas autoimmune hypothyroidism may be relatively more common in mild-to-moderate obesity. Obesity also induces structural changes in the thyroid, including increased volume, hypoechogenicity, and adipocyte infiltration, which may reverse with weight loss. Weight reduction interventions – including dietary strategies, bariatric surgery, and pharmacotherapy – consistently reduce TSH with variable effects on free thyroid hormones. Emerging therapies, such as that with GLP-1 receptor agonists, may influence the HPT axis directly or indirectly through weight loss, although data remain limited. Understanding the interplay between obesity and thyroid function is important for the appropriate interpretation of thyroid function tests, differentiation of adaptive versus pathological changes, and optimization of treatment strategies in patients with excess adiposity.

Keywords: thyroid; obesity; BMI; TSH; GLP-1 receptor agonists; bariatric surgery; diet; weight loss

Introduction

Obesity and thyroid disorders are highly prevalent worldwide and represent major public health concerns. Nearly half of the global adult population (45.1%) is affected by overweight or obesity (1), while thyroid dysfunction affects a substantial proportion of individuals, particularly in Europe, estimated at 3.82% (2). These conditions frequently coexist, and increasing evidence indicates that their association is not merely coincidental. Thyroid hormones are key regulators of energy expenditure, thermogenesis, and lipid metabolism, acting on resting metabolic rate and appetite through central and peripheral pathways (3). As a result, the hypothalamic–pituitary–thyroid (HPT) axis plays a crucial role in body weight regulation and metabolic adaptation. At the same time, excess adiposity can modulate thyroid axis activity. Individuals with obesity often display mildly elevated thyroid-stimulating hormone (TSH) levels in the absence of true thyroid disease (4, 5), suggesting that these alterations may reflect adaptive responses to increased body weight rather than primary thyroid dysfunction.

Considering the multifactorial nature of obesity and its complex interplay with thyroid physiology, this review

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aims to critically review current evidence and highlight emerging topics in the interaction between obesity and the thyroid axis. The main findings of each section are summarized in Table 1.

Table 1 Summary of the main findings of each section.

Main messages
Thyroid function, thyroid autoimmunity and obesity
• Obesity is closely linked to thyroid function, with TSH often rising as BMI increases
• Changes in fT3 and fT4 levels in obesity are inconsistent across studies, due to differences in obesity severity, metabolic status, and other confounders.
• Two hypotheses exist: (1) obesity itself drives TSH elevation independently of autoimmunity, and (2) obesity increases the risk of autoimmune hypothyroidism.
• Evidence suggests non-autoimmune hyperthyrotropinemia predominates in severe/morbid obesity, while autoimmune hypothyroidism may be more relevant in mild/moderate obesity.
• Population and clinical data indicate elevated TSH in obese individuals is often physiological/adaptive, supported for example by normalization after weight loss and favorable lipid profiles
Thyroid function and morbid obesity
• Obesity is heterogeneous, and its impact on thyroid function varies with severity, fat distribution, and metabolic health.
• Morbid obesity is associated with a rightward shift in TSH reference ranges; using normal-weight references can highly increase the apparent prevalence of elevated TSH.
• Obesity sub-phenotypes—metabolically healthy vs. unhealthy—show different thyroid patterns: elevated TSH is more linked to metabolic health than to BMI alone.
Thyroid Morphology and Volume
• Obesity alters thyroid morphology and volume, frequently causing hypoechogenicity on ultrasound and increased thyroid volume
• Histological changes include adipocyte and lymphocyte infiltration, low-grade inflammation, and dysregulation of metabolic pathways.
• Weight loss exceeding 10% can reverse these changes, resulting in reduced thyroid volume, improved echogenicity, and lower TSH, in both adults and children.
Weight-Loss Interventions Influence on Thyroid Function
• Diet-induced weight loss consistently reduces TSH and fT3, while fT4 generally remains unchanged; some evidence suggests that higher baseline TSH may predict a better weight-loss response.
• Bariatric surgery produces effects on thyroid function similar to diet, depending on the procedure; elevated TSH may resolve spontaneously after surgery.
• GLP-1 receptor agonists may reduce TSH, though evidence is limited and mixed; effects may be secondary to weight loss or involve direct hypothalamic/pituitary modulation, with no consistent changes in fT3 or fT4. The impact of newer dual GLP-1/GIP agonists remains unstudied.
• Overall, evidence indicates that weight loss itself leads to a reduction in TSH levels, regardless of the method used to achieve it.

Research strategy

This narrative review is based on a literature search performed in PubMed using keywords including 'thyroid' and 'obesity'. Articles were selected based on their relevance to the topic, with priority given to more recent publications. Additional studies were identified by screening the reference lists of the selected articles.

Thyroid function, thyroid autoimmunity, and obesity

Thyroid function has been extensively investigated in individuals with obesity because of the well-established role of triiodothyronine (T3) in regulating thermogenesis and energy expenditure, as well as its involvement in appetite control, glucose metabolism, and lipid homeostasis (6). It is now widely accepted that obesity and thyroid function are closely interconnected. The classical view supported the notion that thyroid dysfunction – particularly hypothyroidism – may lead to weight gain and obesity (7). This effect may be mediated by multiple mechanisms, including a reduction in basal metabolic rate and thermogenesis, and fluid retention contributing to increased body weight (8).

Nevertheless, increasing evidence indicates that obesity itself can induce significant changes in circulating thyroid function parameters.

The first demonstration that serum thyroid parameters may change following weight gain in humans dates back to more than 40 years (9). More recent studies have consistently reported that serum TSH concentrations increase with rising BMI, both in animal models (10) and in humans (10, 11, 12, 13, 14, 15). However, the mechanisms underlying this elevation in TSH among individuals with obesity remain a matter of debate.

A key observation supporting the hypothesis of a functional, rather than pathological, origin of obesity-related hyperthyrotropinemia is the normalization of serum TSH levels following weight loss (16). This finding suggests that increased TSH secretion may represent an adaptive response of the HPT axis to weight gain especially in view of the notion that variations in free thyroxine (fT4) and free triiodothyronine (fT3) concentrations are by far less consistently observed.

Indeed, some studies report higher fT3 levels in subjects living with obesity (13, 17, 18), whereas others found lower or similar fT3 concentrations (19, 20). Similarly, fT4 levels have been reported to be higher than (13, 21), lower than (12, 19, 22), or similar to (18, 23, 24) those observed in non-obese subjects.

Revisiting the existing literature, two contrasting hypotheses have been proposed to explain the relationship between thyroid function and obesity.

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According to the first hypothesis, obesity per se is responsible for the observed alterations in circulating thyroid parameters – particularly elevated serum TSH levels – independently of autoimmune thyroid disease. In a previous large cohort study of patients with morbid obesity (BMI > 40 kg/m^2) (19), a high prevalence of isolated TSH elevation was observed. Importantly, this abnormality was not associated with the typical features of autoimmune subclinical hypothyroidism, namely i) thyroid autoantibody positivity, ii) female predominance, and iii) a reduced fT4/fT3 ratio.

The alternative hypothesis sustains that individuals with obesity are more prone to develop autoimmune hypothyroidism and that even mild thyroid failure may contribute to progressive weight gain, ultimately leading to overt obesity. Supporting this view, a study by Marzullo *et al.* (24) suggested that obesity represents a risk factor for thyroid autoimmunity, thereby linking excess body weight to the most common cause of acquired thyroid failure. Similar conclusions were reached by a 2019 meta-analysis (25), which showed a significant association between obesity and the presence of Hashimoto's thyroiditis.

Epidemiological data do not uniformly support a clear increase in thyroid autoimmunity among individuals with obesity (21, 26). As shown in Table 2, the pooled analysis of data from the general population – where the prevalence of at least one thyroid autoantibody may reach up to 20% in some cohorts (27, 28, 29, 30, 31, 32, 33, 34) – compared with cohorts of obese subjects does not suggest a higher risk of developing thyroid autoimmunity in obesity.

Moreover, some studies suggest that the positive relationship between TSH levels and BMI would be evident only in patients without thyroid autoimmunity, and not in patients without (35, 36). This finding suggests that, in the absence of thyroid autoimmunity, higher BMI is associated with higher TSH, likely due to adaptive or compensatory mechanisms in obesity rather than true thyroid dysfunction. In contrast, in subjects with autoimmune thyroiditis, the lack of association between TSH and BMI suggests that thyroid autoimmunity overrides or masks the obesity-related adaptive changes in TSH regulation.

In addition, the observed association between thyroid autoimmunity and obesity may be biased by the higher female-to-male ratio shared by both conditions (37, 38). Indeed, in a study including over 5,000 adults (3,448 females and 1,561 males), the effect of obesity on TSH levels was sex-dependent. In particular, females and nonsmokers had higher TSH levels and TSH increased progressively with BMI in females, but not in males (12).

Another possible source of discrepancy in the existing literature stems from the fact that studies reporting an association between obesity and thyroid autoimmunity (24, 25) generally included individuals across a broad spectrum of adiposity, from grade I to grade III obesity. This raises the possibility that autoimmune thyroid disorders (AITDs) may be relatively more prevalent among individuals with mild obesity, potentially reflecting weight gain secondary to true thyroid dysfunction. In contrast, in severe and morbid obesity, elevated serum TSH more frequently appears to reflect non-autoimmune, compensatory mechanisms (19, 39).

Individuals with obesity often undergo screening procedures even in the absence of specific symptoms, which may introduce a selection bias. The substantial increase in obesity prevalence over recent decades has heightened the need for endocrine assessments to identify secondary causes of obesity, such as hypercortisolism and hypothyroidism. Indeed, the latest European Society of Endocrinology guidelines on endocrine screening in obesity recommend screening all patients with obesity for thyroid function (40). In this setting, measuring thyroid autoantibodies is especially important to differentiate isolated hyperthyrotropinemia from autoimmune subclinical hypothyroidism.

However, the distinction between adaptive and pathological TSH elevation remains largely inferential, as most evidence derives from heterogeneous observational, often cross-sectional studies with variable obesity phenotype classification, thyroid function assays, antibody assessment, iodine status, and other potential confounders.

Taken together, neither of the two opposing hypotheses alone adequately explains the complex relationship between thyroid autoimmunity and obesity. The available evidence supports the coexistence of both mechanisms. Autoimmune hypothyroidism may be relatively more prevalent in individuals with mild-to-moderate adiposity, whereas the balance of current evidence suggests that isolated, non-autoimmune hyperthyrotropinemia may be more prevalent in severe and morbid obesity.

Thyroid function and obesity phenotypes

Obesity is a heterogeneous condition, and its impact on thyroid homeostasis varies substantially across the spectrum of disease severity.

According to the most recent clinical guidelines (41), obesity is defined taking into account further anthropometric measures and body composition in addition to BMI. In addition, a distinction has recently been introduced between clinical obesity, defined by the presence of adiposity-related organ dysfunction or physical limitations, and preclinical obesity, characterized by excess adiposity without overt clinical manifestations (42).

In recent years, obesity has been further subclassified based on individuals' metabolic health status.

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Table 2 Rates of antithyroid autoantibody positivity in studies performed in the general population or in subjects living with obesity.

Study	Population	Females	Males
Bjøro *et al*. (30)	General	13.9%	2.8%
Hollowell *et al*. (31)	General	14.6%	8.0%
Zophel *et al*. (32)	General	25.8%	14.4%
Spencer *et al*. (33)	General	23.2%	12.2%
Amouzegar *et al*. (27)	General	16%	8.5%
Keyhanian *et al*. (28)	General	21.2%	8.6%
Shinkov *et al*. (34)	General	23%	10%
Pedersen *et al*. (29)	General	13.1%	4.2%
Michalaki *et al*. (21)	Obese	16.6%*	
Rotondi *et al*. (19)	Obese	14.4%	3.2%
Marzullo *et al*. (24)	Obese	14.5%	2.4%
Temizkan *et al*. (26)	Obese	14%*	

*Includes percentage of both sexes.

Several obesity sub-phenotypes with distinct metabolic profiles have been described, including metabolically healthy non-obese, metabolically healthy obese, metabolically unhealthy non-obese, metabolically unhealthy obese, metabolically unhealthy overweight, and metabolically unhealthy normal weight. It should be noted that definitions of metabolically healthy and unhealthy phenotypes vary substantially across studies, with no universally accepted definition and considerable heterogeneity in the metabolic criteria used (43).

Increasing attention has been directed toward understanding whether alterations in thyroid function are associated with obesity per se or rather with specific metabolic phenotypes.

In a recent study, Kim *et al.* (44) reported no significant association between obesity phenotypes and serum TSH levels, although the metabolically healthy non-obese group exhibited significantly higher fT4 levels than the other phenotypes. In contrast, another study (45) evaluating thyroid function across metabolic phenotypes found that metabolically unhealthy individuals had an increased risk of subclinical hypothyroidism. In particular, individuals in the metabolically unhealthy normal-weight, overweight, and obese groups showed a significantly higher risk of elevated TSH compared with the metabolically healthy normal-weight phenotype.

These findings are consistent with observations from the Tehran thyroid study, which demonstrated that fT4 levels are positively associated with the development of the metabolically healthy non-obese phenotype and negatively associated with the development of the metabolically healthy obese phenotype, whereas TSH levels are positively associated with the development of the metabolically unhealthy non-obese phenotype (46).

Collectively, these studies suggest that subclinical hypothyroidism is more closely related to an individual's metabolic health status than to the degree of obesity itself. A higher fT4 level would instead characterize subjects living with overweight or obesity who are metabolically healthy.

Obesity, thyroid morphology, and thyroid volume

Ultrasound (US) examination of the thyroid has become an invaluable tool for studying thyroid disorders. Under normal circumstances, thyroid parenchyma displays high echogenicity, reflecting its orderly follicular organization (47), while autoimmune thyroid diseases typically produce a markedly hypoechoic pattern (48). Yet, clinical studies have revealed that individuals with overweight or obesity often exhibit thyroid hypoechogenicity despite having no biochemical or cytological evidence of autoimmunity (49). A study by Rotondi *et al.* (19) showed that, although hypoechogenicity was rather frequent among patients living with obesity, only 20.9% of these patients showed both hypoechogenicity and positive thyroid autoantibodies. One proposed explanation is the possibility of intrathyroidal fat accumulation, a hypothesis supported by observations in younger populations. Radetti and colleagues (49) described a surprisingly high prevalence of hypoechoic thyroid patterns in obese children who displayed neither serological markers nor cytological features of autoimmunity. Cytology in these cases was normal – showing colloid and typical thyrocytes without inflammatory infiltrates – strongly implying that the US alterations reflect structural remodeling rather than immunological injury. Histopathological data, although limited to relatively small series, provide additional insights. According to Basolo *et al.* (50), from the histological point of view, obese patients exhibit increased infiltration of adipocytes and lymphocytes within the thyroid parenchyma, but this lymphocytic infiltration is not associated with autoimmune markers or thyroid autoantibodies. The degree of adipocyte infiltration correlates with BMI and is significantly higher in obese compared with normal-weight individuals. Lymphocyte markers (CD45, CD3+, and CD8+) and mast cell scores are also elevated, suggesting low-grade, obesity-related inflammation rather than classic autoimmune thyroiditis. In addition, gene expression profiling revealed upregulation of metabolic and immune-related pathways, including increased leptin receptor expression, which may contribute to altered tissue characteristics and echogenicity. In summary, these findings, even if derived from relatively small and selected cohorts, suggest that obesity-related hypoechoic thyroid echogenicity may be associated with structural changes, such as adipocyte infiltration, low-grade inflammation, and metabolic alterations.

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Importantly, studies on weight loss have shown that these changes may reverse. Sari *et al.* showed that a weight reduction of more than 10% over six months leads to meaningful decreases in thyroid volume and TSH levels, whereas weight loss below this threshold produced no significant effect (20). Similarly, Licenziati *et al.* (51) found that dietary weight loss in obese children and adolescents significantly improved thyroid ultrasound appearance: the echogenicity at ultrasound increased in most participants, and half achieved complete normalization.

Regarding thyroid volume, studies in pediatric populations indicate an association with obesity. For example, Lass *et al.* (52) reported that overweight children had a significantly greater thyroid volume compared with their normal-weight peers. Furthermore, Licenziati *et al.* (51) demonstrated that children undergoing weight loss experienced a significant reduction in thyroid volume in addition to TSH.

However, it is important to note that an increased neck circumference, mainly seen in obese individuals or in those with a short and wide neck, may reduce the quality of the ultrasonographic acoustic window during thyroid volume assessment, making the acquisition of accurate and precise images more challenging. Indeed, ultrasound and ultrasound-guided procedures were reported as more challenging in patients living with obesity (53), even if reports on thyroid ultrasound are lacking.

The obese population is more frequently referred for thyroid ultrasound evaluation, partly due to higher TSH levels; therefore, the higher documented prevalence of thyroid nodules may be influenced by increased imaging and detection. However, available evidence indicates that these imaging differences do not translate into an increased risk of thyroid malignancy. In a comparative study of severely obese and non-obese individuals, no significant differences in suspicious cytology rates were observed when nodules were stratified according to ATA 2015 recommendations and ACR TI-RADS criteria (54). Therefore, obesity per se seems to not modify indications for fine-needle aspiration or follow-up intervals when standardized risk stratification systems are appropriately applied.

Altogether, obesity contributes to structural modifications of the thyroid through mechanisms that include increased gland volume, altered echogenicity, inflammatory micro-changes, and even adipocyte infiltration. More studies are needed to better elucidate the mechanisms underlying lower echogenicity in obese patients.

Influence of weight loss interventions on thyroid function

Evidence-based weight loss strategies include lifestyle modification, dietary interventions, pharmacological therapy, and bariatric surgery. Lifestyle modification is the first-line approach and typically results in a 5–10% reduction in body weight, although long-term maintenance is limited. Bariatric surgery remains the most effective option for severe obesity, achieving the largest and most durable weight loss despite its invasive nature. New pharmacological treatments, particularly GLP-1 receptor agonists and dual GIP/GLP-1 agonists, offer substantial and more sustained weight reduction (55). Weight loss obtained with diet, bariatric surgery, or pharmacological interventions induces relevant changes in the HPT axis and thyroid morphology, as shown in Fig. 1.

Diet-induced weight loss

Dietary intervention represents the first-line approach in the management of overweight and obesity. Current guidelines (56, 57) recommend a reduced-calorie diet for weight loss in adults with overweight and obesity, without endorsing a single specific dietary pattern. Several studies conducted in both pediatric and adult populations have demonstrated that diet-induced weight loss is associated with adaptive modifications of the HPT axis. The most consistent hormonal pattern observed is a reduction in TSH and fT3 levels, while fT4 concentrations generally remain unchanged, both in adults (58, 59) and in children (15, 51). Moreover, recent evidence suggests that higher baseline TSH levels may predict a more successful weight loss response following dietary intervention (60).

The ketogenic diet, characterized by substantial carbohydrate restriction alongside increased fat and protein consumption, appears to modify peripheral thyroid hormone levels. In a study by Iacovides *et al.* (61), comparing a high-carbohydrate, low-fat diet with a ketogenic diet, a significantly greater reduction in plasma T3 concentrations was observed after weight loss. Conversely, thyroxine (T4) levels significantly increased following the ketogenic diet, while no significant changes were noted after the high-carbohydrate, low-fat diet; TSH levels were unaffected by diet type. Consequently, the T3:T4 ratio was significantly higher after the high-carbohydrate, low-fat diet, suggesting enhanced peripheral conversion of T4 to T3 in the presence of higher carbohydrate availability. Additional evidence suggests that ketogenic diet may exert differential effects depending on baseline thyroid function. In pediatric patients treated with a ketogenic diet for intractable epilepsy, a greater increase in serum TSH was observed in those with elevated baseline TSH, without associated changes in thyroid ultrasound findings (62).

The Mediterranean diet (MD) has also been proposed to influence thyroid hormone homeostasis (63). Zupo *et al.* investigated the relationship between MD adherence and thyroid function in 324 euthyroid overweight and obese individuals from Southern Italy, demonstrating an

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inverse association between MD adherence and circulating fT3 and fT4 levels. Notably, higher consumption of extra-virgin olive oil was specifically associated with lower fT3 and fT4 concentrations. After adjustment for sex, age, and body mass index, only the association between fT4 levels and MD adherence remained significant in logistic regression analyses, while no effect on serum TSH was detected (64).

Surgery-induced weight loss

Studies performed in patients undergoing bariatric surgery provides further evidence for the impact of weight loss on thyroid function. Some studies (65, 66, 67, 68, 69) demonstrated significant postoperative reductions in fT3 and TSH, accompanied by an increase in fT4, at 6 and 12 months following laparoscopic sleeve gastrectomy, gastric banding, or Roux-en-Y gastric bypass (RYGB). A meta-analysis by Guan *et al.* (70) indicated that bariatric surgery results in reductions in TSH, fT3, and total T3, whereas fT4, total T4, and reverse T3 generally remain unchanged. More recent data (71) confirm significant postoperative decreases in TSH and both free and total thyroid hormone fractions, also demonstrating a direct correlation between fat mass reduction and the magnitude of TSH decline. In 2025, a systematic review and meta-analysis (16) including studies on both caloric restriction and bariatric surgery confirmed that weight reduction is consistently associated with decreased TSH, decreased fT3, and increased fT4 levels. However, it should be noted that most available evidence derives from observational studies with heterogeneous surgical procedures, variable follow-up durations, and relatively modest hormonal changes, which frequently remain within the reference range.

Only a few clinical studies compared the effects of different surgical interventions on the HPT axis. Seighali *et al.* demonstrated a significant reduction in T3 levels after RYGB compared with other bariatric procedures; however, no significant differences among surgical techniques were observed with respect to TSH reduction at 12 months postoperatively (72). In contrast, Najjari *et al.* demonstrated a higher rate of resolution of subclinical hypothyroidism with SG compared with one-anastomosis gastric bypass (73).

These changes may also have important clinical implications, as bariatric procedures can alter requirements and absorption of levothyroxine therapy, necessitating careful postoperative monitoring and dose adjustment. On the one hand, impaired drug dissolution and absorption – related to increased gastric pH and reduced gastric volume – may decrease bioavailability. On the other hand, substantial weight loss may lead to a decreased hormone requirement (74, 75, 76).

Drug-induced weight loss

The remarkable increase in the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in recent years has drawn attention to a class of drugs that have proven to be highly effective in managing type 2 diabetes mellitus and also mitigating the occurrence of diabetes-related complications. These drugs, acting as agonists of glucagon-like peptide-1 receptor (GLP-1R), are recognized for promoting insulin secretion, suppressing glucagon release, and delaying gastric emptying (77). However, while the beneficial effects of GLP-1 RAs on glycemic control, weight loss, and blood pressure reduction are extensively documented, a crucial aspect requiring further investigation is their impact on thyroid function.

Notably, available evidence indicates that GLP-1 RA (liraglutide) induces clinically meaningful and comparable weight loss in individuals receiving levothyroxine for well-controlled hypothyroidism and in those without thyroid disease, with similar changes also observed in body composition (78).

Basic studies suggest that there could be possible direct impacts of GLP-1R activation on the HPT axis, although the exact mechanism and outcomes are still being elucidated (79).

GLP-1 RAs may have a direct central inhibitory effect, as GLP-1Rs are expressed in the paraventricular nucleus (PVN) of the hypothalamus where thyrotropin-releasing hormone (TRH)-producing neurons are located. This suggests that GLP-1 RAs may directly influence the activity of TRH-producing neurons in the hypothalamus (80). Experimental evidence on animals supports a link between the GLP-1 system and the HPT axis. Ruska *et al.* demonstrated that GLP-1R activation modulates TRH-producing neurons in the hypothalamic PVN, while Beak *et al.* showed that GLP-1 directly stimulates TSH secretion by acting on α-TSH cells in the pituitary, indicating that GLP-1 may influence thyroid regulation at both hypothalamic and pituitary levels (81, 82). In addition, the reduction in serum TSH levels is unlikely to be due to a direct effect on the thyroid gland itself because GLP-1Rs are primarily expressed in the C cells of the thyroid, which are not responsible for thyroid hormone synthesis (83). However, these findings are derived from preclinical models and their clinical relevance in humans remains uncertain.

In contrast, in clinical studies, the observed changes in TSH may also be explained by weight loss-related metabolic effects rather than direct pharmacological action. There are not many clinical studies that have examined the effect of GLP-1 RAs on thyroid function, and it is important to note that evidence on GLP-1 receptor agonists and the HPT axis derives mainly from experimental studies and small clinical trials, predominantly in patients affected by type 2 diabetes or NAFLD and not just by obesity.

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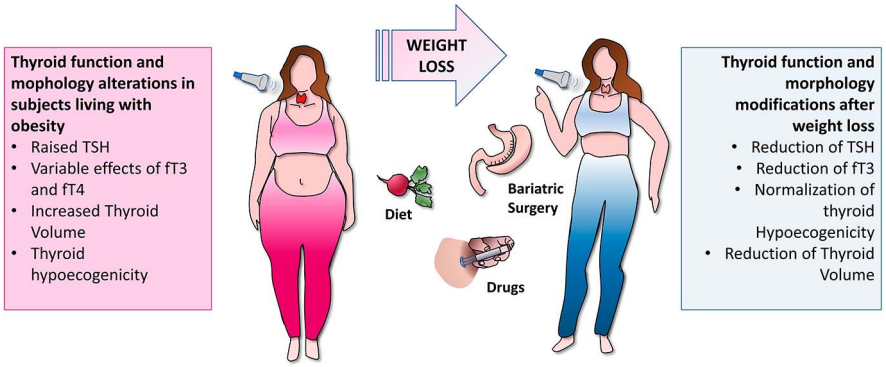

Figure 1

Thyroid function and morphology alterations observed in subjects living with obesity and their modifications after weight loss.

Sencar *et al.* (84) conducted a study on 46 patients with diabetes treated with exenatide and found a significant reduction in serum TSH concentration without a significant change in fT4 and fT3 before and after treatment. The same result was observed in 39 obese patients with diabetes treated with exenatide for 6 months in Köseoğlu *et al.*'s study (85) with no significant changes in fT3 and fT4 levels over time. Ye *et al.* (86) demonstrated in a population of 49 diabetic patients with non-alcoholic fatty liver disease that treatment with liraglutide reduced TSH levels.

The mechanisms underlying TSH reductions are still debated. Tee *et al.*'s study (87) suggests that TSH decreases are solely secondary to weight loss induced by the drug, whereas the study of Sencar and colleagues (84) found no significant correlation between weight loss and TSH, reporting reductions in TSH even in the absence of significant weight loss, implying a possible direct pharmacological effect on the HPT axis.

Studies attempting to disentangle drug-specific effects from caloric restriction include the study by Byun *et al.* (88), which compared semaglutide treatment with pair-fed rats. In the study, it was shown that semaglutide had minimal effects on the thyroid axis. Despite increased DIO2 expression in adipose tissues, circulating TSH and thyroid hormones remained largely unchanged. In male rats, TSH, fT3, and fT4 levels were unaffected by semaglutide. In female rats, feed restriction reduced circulating T4, an effect prevented by semaglutide, while TSH and T3 remained unchanged. Overall, semaglutide did not induce clinically relevant alterations in TSH, fT3, or fT4, indicating preserved systemic thyroid hormone homeostasis.

In a study by Zhang *et al.* (89), the main finding was a statistically significant reduction in fT4 levels within the GLP-1 RA group compared with baseline; however, when comparing the change in fT4 between the GLP-1 RA group and the control group, no significant difference was observed. For fT3 and TSH, the study found no significant changes either within groups or between groups. Subgroup analyses stratified by sex, age, and disease duration also confirmed the absence of significant effects of GLP-1 RA therapy on these thyroid parameters.

Table 3 Summary of studies regarding modifications in the hypothalamus–pituitary–thyroid function after weight loss.

Study	Study design	Weight loss intervention		Changes in thyroid function
Liu *et al.* (59)	2-year RCT	Diet	Hypocaloric diet	↓ TSH, ↓ FT3, unchanged FT4
Licenziati *et al.* (51)	PS	Diet		↓ TSH, unchanged FT4
Iacovides *et al.* (61)	RCCS	Diet	KD vs HCLF	↓ T3, ↑ T4, unchanged TSH
Kose *et al.* (62)	PS	Diet	KD	↑ TSH
Zupo *et al.* (64)	CSS	Diet	MD (higher consumption of extra-virgin olive oil)	↓ FT3 e FT4
Dall'Asta *et al.* (65)	PS	Bariatric Surgery	Gastric banding	↓ FT3, ↑ FT4 and unchanged TSH
Ruiz Tovar *et al.* (69)	RS	Bariatric Surgery	SG	↓ TSH
Tian *et al.* (71)	RS	Bariatric surgery	SG and RYGB	↓ TSH, FT3, T3 T4, FT4
Najjari *et al.* (73)	RS	Bariatric Surgery	SG vs OAGB	↓ TSH, unchanged FT4
Sencar *et al.* (84)	PS	Pharmacotherapy	GLP-1 RA (exenatide)	↓ TSH, unchanged FT3 and FT4
Köseoglu *et al.* (85)	PS	Pharmacotherapy	GLP-1 RA (exenatide)	↓ TSH, unchanged FT3 and FT4
Ye *et al.* (86)	RS	Pharmacotherapy	GLP-1 RA (liraglutide)	↓ TSH
Tee *et al.* (87)	PS	Pharmacotherapy	GLP-1 RA (exenatide)	↓ TSH, unchanged FT4
Zhang *et al.* (89)	MRPS	Pharmacotherapy	GLP-1 RA (any)	↓ FT4

RCT, randomised clinical trial; PS, prospective study; RS, retrospective study; RCCS, randomised crossover-controlled study; CSS, cross-sectional study; MRPS, Mendelian randomization and prospective study; KD, ketogenic diet; HCLF, high–carbohydrate low–fat; MD, Mediterranean diet; SG, sleeve gastrectomy.

Concerns have been raised regarding a potential association between GLP-1 RAs and thyroid cancer, primarily based on preclinical studies showing C-cell hyperplasia and medullary thyroid carcinoma in rodents, likely due to GLP-1 receptor expression in thyroid C cells. However, current evidence from large studies in humans does not support an increased risk of thyroid cancer in patients treated with GLP-1 RAs (90, 91, 92).

To our knowledge, no studies have yet evaluated the effects of GLP-1/GIP RAs (tirzepatide) on thyroid function.

The main studies on the effects of weight loss interventions on the HPT axis are summarized in Table 3.

In conclusion, the evidence regarding the effects of GLP-1 on thyroid function is limited and controversial; indeed, other studies mainly focusing on the occurrence of thyroid diseases suggest that the activation of GLP-1R does not induce the de novo occurrence of thyroid dysfunction (93).

Conclusion

The dynamic interplay between the thyroid gland and adipose tissue is fundamental to the regulation of body weight and overall energy homeostasis. Although obesity clearly influences thyroid physiology, its exact pathogenic role in thyroid disease remains an area of ongoing investigation. Evidence summarized in this review highlights the complexity of thyroid responses across different degrees of obesity and during weight loss, as well as the variability in TSH and thyroid hormone adaptations. Importantly, while treating overt and subclinical hypothyroidism remains crucial for cardiovascular and metabolic health, current data do not support pharmacological intervention for the isolated, mild hyperthyrotropinemia frequently observed in obese individuals. Recognizing these nuances is essential for informed clinical decision-making and for avoiding unnecessary treatment in cases where thyroid alterations may reflect adaptive responses rather than true glandular dysfunction.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

LC, IC, RP, and SAMDI wrote the manuscript. LC and MR critically reviewed the manuscript. All authors approved the version to be published.

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